Head and Neck Cancer Research and Support Foundations

Joshua E. Lubek, MD, DDS

KEYWORDS

• Head and neck cancer research • Dysplasia • Immunotherapy • Xerostomia • Cancer organizations

KEY POINTS

- Ongoing genetic and epigenetic research involving DNA methylation, salivary biomarkers, wild-type p53 tumor suppressor gene proteins, and HPV oncogenes are being directed at identification and treatment of dysplastic and malignant squamous cell mucosal lesions.
- Research is being conducted to improve immunotherapy drug response rates by increasing the amount of inflammation within the tumor microenvironment.
- Ongoing research is focused on the application of the antidiabetic drug metformin for the prevention and management of oral squamous cell dysplastic lesions.
- The use of stem cells for the prevention and management of salivary dysfunction secondary radiotherapy is being investigated.
- Professional and nonprofit cancer support organizations are essential for furthering education and research within the area of head and neck cancer.

INTRODUCTION

The term head and neck cancer encompasses a large cohort of varied tumor pathologic conditions that can arise within the structures/subsites of the head and neck. Head and neck cancer ranks as the sixth most common type of cancer worldwide with head and neck squamous cell carcinoma (HNSCC) accounting for approximately 90% of all cases. It represents a significant global health concern because patients often present with advanced stage disease requiring extensive multimodality therapy (surgery, radiation, and chemotherapy). Patients often experience debilitating posttreatment side effects that affect quality of life as related to speech, swallowing, and cosmetic concerns. Many patients are unable to return to the workforce and are left on chronic disability.[1] Recurrence of disease is also of significant concern especially in those patients with advanced stage disease. The locoregional recurrence rates are approximately 40% with distant metastases occurring in 20% to 30% in this advanced stage cohort. This impact on patient recovery and function underscores the importance of both government and industry help to support research in the field of head and neck cancer. It also highlights the need for access to resources for patients and their families for their physical and emotional demands throughout their cancer care.

The vast number of research projects, published scientific abstracts/papers, and current clinical trials available within the discipline of head and neck cancer is obviously far too extensive to even attempt to summarize within this article of the *Oral and Maxillofacial Surgery Clinics of North America*. The purpose of this article is to provide

Disclosure: The author has nothing to disclose.
Oral–Head and Neck Surgery/Microvascular Surgery, Department of Oral and Maxillofacial Surgery, University of Maryland, 650 West Baltimore Street, Suite 1401, Baltimore, MD 21201, USA
E-mail address: jlubek@umaryland.edu

Oral Maxillofacial Surg Clin N Am 30 (2018) 459–469
https://doi.org/10.1016/j.coms.2018.06.007

a brief review of selected research topics in the specialty of HNSCC covering areas of cancer prevention, detection, surgical technologies, immunotherapy, genetics, and treatment sequelae. Various research foundations/resources available to those patients undergoing HNSCC and clinicians/researchers with an interest in HNSCC are also reviewed.

GENETIC AND EPIGENETIC RESEARCH

Numerous environmental events, such as the exposure to tobacco-associated carcinogens, ultraviolet light, and chronic viral infections, can result in both genetic and epigenetic changes leading to tumor development and disease progression. Genetic changes include events that lead to irreversible alterations in cellular DNA sequences, such as gene deletions, amplifications, and mutations, that damage tumor suppressor genes or activate oncogenes. Epigenetics refers to external modifications to DNA resulting in the inability for the cell to understand the genetic information. They are potentially reversible or transient modifications.[2–5]

DNA-methylation is one such epigenetic event that transfers a methyl group to the C-5 position of the cytosine ring of DNA by specific DNA-methyltransferases. The loss of heterozygosity of hypermethylated genes is often involved in tumor angiogenesis and the metastatic potential of HNSCC. Numerous hypermethylated genes identified within HNSCC involve cell-cycle control, programmed cell death, cell-cell interactions, and DNA repair mechanisms.

Tumor suppressor protein 53 (p53) responds to cell stress that arrests cell cycle and promotes DNA repair. Loss of p53 function results in human malignancy with more than 50% of observed HNSCC having p53 mutations identified within their cell DNA.

Methods of rapid, cost-effective identification of DNA-methylation patterns or p53 mutations are being studied to help identify potentially aggressive dysplastic lesions or in the use of intraoperative margin assessment. Brennan and colleagues[6] were the first group to identify p53 mutations using polymerase chain reaction (PCR) analysis at histologically negative surgical margins evaluated by pathologists using standard hematoxylin-eosin staining in a series of patients treated for oral squamous cell carcinoma. Interestingly, 38% of those with altered p53 mutations developed recurrence as compared with none without the mutation. This article was one of the first to explain why patients with so-called negative margins could develop local recurrence.

Limitations to the use of molecular markers of methylation for intraoperative margin assessment include the myriad of mutations that occur within a tumor creating difficulties in isolating those markers that are of highest risk for potential recurrence or transformation and the amount of time needed to analyze the data. Currently, no tests are available to be performed during the immediate operative procedure.[7]

Treatment of dysplasia and HNSCC through the use of gene therapy by introducing a wild-type p53 gene is currently under investigation. The wild-type p53 gene is an integral cancer suppressor gene that maintains genomic integrity by the production of a protein that arrests the cell cycle and stimulates DNA repair and cell apoptosis.

Introducing the p53 gene into the target cell is challenging. Viral vectors involve replacing a portion of the virus genome with a desired genetic sequence. The virus is injected into tumor cells and allowed to infect different cell types spreading the desired sequence. Of particular research interest is the use of modified adenoviruses. Adenoviruses are composed of DNA, unlike retroviruses, which are composed of RNA. Adenoviruses are not integrated into the host genome and do not cause any change to the host germ cell lineage.[8,9] One of the earliest research trials involving the use of gene therapy was described by Clayman and colleagues[10] in 1998, whereby the investigators injected an adenovirus vector p53 into 17 HNSCC patients with unresectable disease. Significant tumor response was reported in 47% of the cohort. A recent trial of advanced stage cervical cancer treated with recombinant human adenovirus-p53 and chemotherapy demonstrated a 95% efficacy with significant tumor shrinkage as compared with the chemotherapeutic arm.[11]

Routes of administration for recombinant adenovirus-p53 (rAD-p53) include intratumoral injection, perfusion, and intravenous injection. Good locoregional responses have been demonstrated in phase 2 trials for patients with HNSCC with combined radiotherapy and intratumoral rAD-p53. However, rAd-p53 alone has not been very successful in achieving complete responses. Intratumoral injection delivers the adenovirus to its target with good local effects and with less toxicity in comparison to the other routes of delivery. The spread of the rAD-p53 from the intratumoral injection site is limited, which limits its ability to affect more distant disease. Intra-arterial injection has been evaluated with good results; however, it does increase the risk of side effects, such as flulike symptoms and bone marrow suppression.[12,13] In a 2014 Chinese randomized placebo-controlled, double-blinded